REMARKS/ARGUMENTS

The non-final Office Action dated 12/13/2007 rejected claims 1-4 and 6-8. Claims 1-4 and 6-8 are pending. No claims are amended.

It is noted that page 6 of the Office Action states that 'THIS ACTION IS MADE FINAL." Since the Office Action Summary states that the action is non-final, and an RCE was just granted, it is assumed that the Office Action is in fact non-final.

Turning now to the Detailed Action, the following remarks are set forth and responded to in the same order as presented in the Office Action.

Rejections Maintained

1. Rejection of Claims under 35 USC §103(e) over Sportsman et al. (US 6,806,053) in view of Iwasaki et al. (J. Biol. Chem. 2002) and Hirata et al. (J. Biol. Chem. 1990)

The Official Action rejects claims 1 – 4 and 6 – 8, the only claims under consideration under 35 U.S.C. §103(a) based on Sportsman, Iwasaki and Hirata. The Office Action states:

> Sportsman et al., in a cell-signaling assay of inositos-phospholipid signaling pathway, disclose detection of intermediate 1, 4, 5 IP_3 of the signaling pathway. The assay include a tracer from the intermediate (i.e. tracer of 1,4, 5 IP_3) and a specific binding partner for 1,4,5 IP_3 (intermediate) and the tracer (e.g. labeled 1,4, 5 IP_3). Sportsman et al. also disclose that the tracer may include a luminophore attached by a suitable chemistry to the intermediate (e.g. a fluorescein succinyl- labeled IP_3) (column 20, example 14 and figs. 5, 6, 7A, 7B, 8A and 8B). Sportsman et al. disclose that specific binding partner generally comprises any compound capable of specifically and competitively binding an analyte and an associated tracer and also disclose that fragments, derivatives or analogs of a preferred specific binding partner may be used (column 11, lines 22-35).

Sportsman et al., however, do not disclose IP_3R receptor or fragments thereof as specific binding partner in this assay.

Iwasaki et al. disclose IP_3R antagonists that strongly and specifically bind to IP_3 (analyte). Iwasaki et al. also disclose N-terminal ligand binding domain of mIP_3R1 comprising amino acid sequence 226-578 as the core region for high affinity binding to IP_3 and the binding affinity is approximately 1000 times greater than that of endogenous IP_3T (see page 2764, left column, lines 6-21). *Since a specific and a strong binding partner for IP_3 is disclosed by Iwasaki et al., it would have been obvious* at the time of the invention to a person of ordinary skill in the art *to include core region of the IP_3R as taught by Iwasaki et al* in the assay method of Sportsman to effectively measure IP_3 in a sample with a reasonable expectation of success because specific binding partner for IP_3 is envisaged in the method of Sportsman et al. (emphasis supplied)

Furthermore,

"Hirata et al. disclose a series of 1 ,4,5-triphosphate (IP_3) analogs with substituents at 2 hydroxy position and disclose that such modification (substitution at 2-hydroxy position) do not substantially interfere with the affinity of IP_3 for IP_3 receptor (see abstract and page 8404, right column, lines 6-13). Therefore, given the above fact that 2-hydoxyl position of IP_3 can be substituted with organic groups without significantly affecting binding affinity of IP_3 for its binding partner (Hirata et al.), it would have been obvious at the time of the invention to a person of ordinary skill in the art to attach luminophore at the 2-hydroxy position of IP_3 in the IP_3-luminophore conjugate as suggested by Sportsman et al with a reasonable expectation of success because attachment by a suitable chemistry is disclosed by Sportsman et al. and substitution at the 2 hydroxyl position know for IP_3, which does not affect IP_3 binding affinity to its binding partner."

In "Response to Arguments," it is stated,

"Therefore, Sportsman et al. disclose strong motivation to include IP_3 binding partners or fragments thereof in the assay methods. Iwasaki's reference is combined with Sportsman et al. because Iwasaki et al. disclose a potential binding partner for IP_3 (i.e. IP_3 receptor or fragment of IP_3R) and disclose that N-terminal 226-578 amino acid sequence of mIP_3R1 binds IP_3 with high affinity and thus would be obvious to try as a binding partner in the method as taught by Sportsman et al. for detection of IP_3. Hirata's reference is combined with Sportsman because Sportsman et al. envisioned IP_3 tracer in the competitive immunoassay method (i.e. IP_3

labeled with a detectable molecule) and Hirata et al. disclose 2 hydroxyl position of IP_3 as a potential position for substitution with an organic group that do not substantially affect the affinity of IP_3 for IP_3 receptor and thus one of ordinary skill in the art would obviously try to link detectable molecules at that position (i.e. 2-hydroxyl position) as this position is a potential position for substitution that does not significantly interfere with binding to it's binding partner."

Response

The Office Action apparently quotes at length from MPEP 2141 "Examination Guidelines for Determining Obviousness under 35 U.S.C.§ 103." These guidelines are intended to provide an appropriate supporting rationale for obviousness rejections in view of the recent decision by the Supreme Court in *KSR International Co. v. Teleflex Inc.* 550 U.S. ___, 82 USPQ2d 1385 (2007).

Combination of references

It is submitted that for references to support an obviousness rejection, it must follow that one would have a reasonable expectation of success in the proposed modification or combination. In addition, the standard of "obvious to try" has very limited applicability. As stated in MPEP 2141, it is limited to situations where there is a "finite number of identified, predictable solutions, with a reasonable expectation of success." That is, it cannot be assumed that a patent applicant has infinite resources to try every possible permutation and combination. In the usual situation, there will be some basis for investing the time and money to conduct research in a certain area. Thus, it cannot be expected that applicants show that cited art "teaches away" from the invention being claimed.

"Sponge protein" (truncated receptor) and high affinity for substituted IP_3

The above discussion is relevant to the fact that, based on the references, there was no reasonable certainty of success in combining the selected portions of the various teachings. First, there is the issue that Iwasaki does not show that the derivative of IP_3 at

the two-position binds to the truncated receptor. As is reported by Iwasaki, the truncated receptor has about a 1000 greater affinity for IP_3 than the natural receptor. Binding affinity is based on a number of effects: hydrogen binding, dipole interactions, charge interactions, steric interactions, van der Waal forces, and changes in conformation of the protein. As is reported in the literature, a protein will naturally have a large number of conformations with various energy barriers between the conformations. One belief is that the ligand captures the conformation that has the highest binding affinity and locks that conformation. It would be expected that the population of the conformations of the naturally occurring IP_3R would be different from the truncated IP_3R receptor. Therefore, one cannot predict with any reasonable certainty what the effect would be of modifying IP_3 by substituting the hydrogen of the hydroxyl at the 2-position with a label. Therefore, determining that the "sponge protein" would retain its high affinity for the substituted IP_3 was not predictable from the available data.

Use of derivatives of IP_3

The Official Action makes the erroneous statement, quoted above, "Since a specific and a strong binding partner for IP_3 is disclosed by Iwasaki et al., it would have been obvious at the time of the invention to a person of ordinary skill in the art to include core region of the IP_3R as taught by Iwasaki et al in the assay method of Sportsman to effectively measure IP_3 in a sample with a reasonable expectation of success because specific binding partner for IP_3 is envisaged in the method of Sportsman et al." The subject assay does not use IP_3 in its assay, but rather a derivative of IP_3. Furthermore, no one had shown that the truncated receptor would have the same high affinity for a derivative of IP_3 at the 2-position that the truncated receptor had for the naturally occurring IP_3.

Hirata and derivatization of IP_3

Hirata is reputed to show that substitution at the 2-position of IP_3 does not interfere with the binding with the naturally occurring IP_3R. First, in light of the above discussion the truncated IP_3R is not the naturally occurring IP_3R, so one must extrapolate that a

modified receptor that has an enhanced affinity of 1000 over the naturally occurring would still have the same affinity for a derivative of IP_3.

In the Official Action it is suggested that there are only 3 positions for derivatization. In fact, there are at least 6 positions, as the phosphate groups can also serve for derivatization. Secondly, this ignores that one can derivatize the carbon atoms to which the groups are attached in IP_3. In addition, one could use pyrophosphates as the bridge to the derivative and replace the hydroxyl groups with a large variety of other groups. In light of Hirata one might have chosen the 2-position as the departure point. However, the subsequent analysis of Hirata indicates that Hirata was not a good source of information as to what to expect in binding of the IP_3 derivatives to the naturally occurring receptor, no less the truncated version.

In the last response, applicants pointed out that the Hirata data do not support Hirata's conclusions. As an expedient, the previous arguments are set forth again here for the Examiner's convenience.

Teaching of Hirata

Hirata prepares derivatives of IP_3 and performs an assay for binding to rat cerebellum homogenate obtained as a dispersed pellet using radioactive IP_3 as the tracer. There is no characterization of the homogenate as to the inositol phosphate receptors, the degree of non-specific binding of IP_3 and the analogs, and the specificity for IP_3R as compared to other proteins that bind IP_3. Therefore, it is greatly a matter of conjecture as to what is occurring in Hirata's assays. The procedure is a simple competition between hot IP_3 and cold IP_3 or IP_3 analogs. The assay determines how much of the hot IP_3 remains bound to the microsomes retained by a glass fiber filter.

Looking at Table 6, indicated as a displacement assay, but really a competition assay, the dark round circles are the competition between the hot and cold IP_3. When the concentration of the two components is the same, only about 10% of the hot IP_3 is captured by the column. This suggests that the microsomes have an excess capacity for the IP_3, since

if there was an inadequate capacity, then one would expect about 50% of the hot IP_3 would be retained as compared to the amount retained in the absence of the cold IP_3. The scale would appear to be a log scale that smoothes out the scatter and provides for some linearity. One cannot evaluate differences in binding of the various IP_3 entities to different binding sites from the log scale.

One would expect that the hot IP_3 would compete equally with the cold IP_3 for the binding sites of the IP_3R and other sites to which IP_3 binds. There are different binding affinities between the isoforms of IP_3 and significant cross-reactivity with other receptors that bind different phosphorylated derivatives of inositol. See, Vanlingen, et al 2001 Biochem Pharmacol 61, 803-9, Yamamoto-Hino 1994 Receptor Channels 2, 9 – 22 and Staudman et al 1988 Biochem J 255, 677 – 83. While there would appear to be no difference between the cold IP_3 and its analogs in competing off the hot IP_3, we do not know what binding sites are being competed off by these entities. Nor do we know to what extent non-specific binding is occurring, where non-specific binding would be expected to be readily displaceable.

It is noted that the L-isomers have little or no effect. This would suggest that there is specific binding of the IP_3 and its analogs, rather than looking at a mass effect. However, there is no certainty as to what the various entities are binding to, except that there seems to be a concentration effect. That at 10 x the amount of analog as compared to hot IP_3 one observes about a 50% reduction in binding of the hot IP_3, is not showing a strong competitor, regardless of what the two compounds are binding to. For an assay, one needs a substantially high affinity in order to have sensitivity and be able to measure low amounts of the analyte.

Finally, there is no knowledge as to what other proteins may be present that could affect IP_3 and the analogs. For example, esterases could hydrolyze the analogs leaving only IP_3, which could be further hydrolyzed by phosphatases. The analogs could be hydrolyzed by phosphatases. There are no controls to determine the fate of the analogs.

What does the example teach? What is reasonably taught by the example is that a homogenate of rat cerebellum—known to have IP_3R and many other receptors for other IP analogs—will bind to IP_3 and derivatives at the 2-position of IP_3 or the hydrolytic products thereof. The large number of available sites in the homogenate, the relatively low affinity that IP_3 has for the different isoforms of IP_3R, and the possibility of modification of the IP_3 and its analogs by enzymatic reactions, makes the data very difficult to analyze.

Declaration

In support of the above position that Hirata does not support the allegations in the Official Action, a declaration under 37 CFR §132 is provided by Dr. Edwin Ullman, an expert in the field of binding assays and a consultant to the assignee of the subject invention. A curriculum vitae accompanies his remarks. Dr. Ullman's conclusions support the conclusion that there is insufficient evidence from the experimental data to conclude that the 2-position derivatives of IP are binding to the IP_3R, no less than the sponge protein with its much higher binding affinity.

Conclusion

As originally stated, combining the references cited by the Official Action gives no reasonable expectation of success. Rather, using the subject application as a road map, these references are found and given a weight that is totally disproportionate to their disclosure. As the courts have repeatedly said, one may not pick and choose from a reference. One must consider the reference in its entirety. Hirata does not support the conclusions that Hirata draws. The data are too ambiguous at best to draw conclusions that the 2-derivative of IP_3 is binding to the various proteins. Without this showing, Hirata is inadequate to suggest the subject invention, that one can prepare a 2-derivative of IP_3 and expect that it would bind to the IP_3 receptor, and even farther afield is the sponge protein.

In view of the above remarks and accompanying declaration, the Examiner is respectfully requested to withdraw the rejections of claims 1-4 and 6-8 and pass this application to issue. If the Examiner believes that the prosecution could be expedited by a

telephonic interview, the Examiner is respectfully requested to call Bertram Rowland, Reg. no.20,015 at (650) 344 4674.

Respectfully submitted,

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